Remarks

In an Office Action issued February 5, the Examiner set forth several grounds of rejection under 35 USC § 112. These matters are addressed separately herein.

Rejections under 35 USC § 112

Claims 1 through 12 were rejected under 35 USC § 112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to use the invention. According to the Examiner, the protein encoded by the isolated nucleic acid described in the specification is what is termed an "orphan protein" in the art. The Examiner goes on to state that there is little doubt that after compete characterization, the DNA and encoded protein may be found to have a specific and substantial credible utility, but asserts that this further characterization is part of the act of invention and until it has been undertaken, applicant's claimed invention is incomplete. The Examiner further asserts that because the instant specification does not teach a biological activity of IL-1 delta, which would support a practical utility, one would not believe that administering the peptide would prevent or treat a condition or disease. Applicants respectfully disagree.

At the outset, applicants note that the claimed invention is not a protein at all, but a method of using a protein. Applicants respectfully disagree with the Examiner's characterization of IL-1 delta as an "orphan" protein. IL-1 delta is a member of the IL-1 superfamily, which is involved in modulating the inflammatory process. Moreover, Applicants have asserted that a soluble version of IL-1 delta may act as an antagonist of other, active cytokines, in the same way that IL-1ra is an antagonist of the actions of IL-1 alpha and IL-1 beta (substitute specification, page 8, lines 5 and 6). Applicants respectfully submit that action as an antagonist is a biological activity that clearly supports a practical utility for IL-1 delta polypeptides. As objective evidence of the activity of IL-1 delta as antagonist, applicants are submitting herewith as Exhibit 1, a publication by Debets et al. (*J. Immunol.*, 2001, 167:1440-1446), in which the investigators found that IL-1 delta antagonizes the activity of another IL-1 family member, referred to therein as IL-1 epsilon, which activity is mediated by binding to a receptor referred to as IL-1R6 (a member of the IL-1 receptor family). Thus, one of ordinary skill in the art of treatment of inflammatory or autoimmune disease (which is quite high) would find that IL-1 delta has a practical utility as an antagonist.

Moreover, a specification which contains a teaching of the manner and process of making and using an invention in terms corresponding in scope to those used in describing and defining the subject matter sought to be patented must be taken as in compliance with the enabling requirement of the first paragraph of 35 USC, § 112, unless there is a reason to doubt the objective truth of statement contained in the specification (*In re Marzocchi and Horton*, 169 USPQ 367; CCPA 1971). Applicants have taught that IL-1 delta may act as an antagonist of other, active cytokines, in the same way that IL-1ra is an antagonist of the actions of IL-1 alpha and IL-1 beta, and Debets et al. confirm this antagonistic activity. To determine optimal dosages, preferred routes of administration and the pharmacokinetic characteristics of an antagonist such as soluble form of IL-1 delta is a matter of routine experimentation for one of ordinary skill in the art. There is no reason to doubt the objective truth of the statements contained in applicants' specification; accordingly, applicants request that the rejection be withdrawn.

Claims 1 through 9 were rejected under 35 USC § 112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to use the invention. According to the Examiner, the claims are directed to a method of treating an individual afflicted with an inflammatory or autoimmune condition by administering IL-1 delta polypeptide. However, the Examiner asserts, the instant specification fails to describe the entire genus of proteins encompassed by the claims in such a way as to reasonably convey to one skilled in the art that, at the time the application was filed, applicants had possession of the claimed invention. Applicants respectfully disagree.

Applicant respectfully submits that in the art of molecular biology the level of ordinary skill is very high and knowledge of a variety of sophisticated techniques and methods is presumed. Moreover, the PTO has made it clear that the teaching required to support claims encompassing a number of molecules which are further limited by reciting an operable activity, is satisfied if the disclosure teaches how to make a candidate molecule and how to test the candidate molecule for the activity. *Ex parte Mark* 12 USPQ2d 1904 (Bd. Pat. App. & Int'f 1989). Since the specification, in combination with the knowledge of those skilled in the art, teaches how to make IL-1 delta polypeptides (including polypeptides that are 80% identical to that of SEQ ID NO:4 and that possess the function of being able to block an inflammatory response) and the specification teaches how to test for blocking activity in

an inflammatory response, the specification enables the subject claims. Any requirement that Applicant limit the claims to specific embodiments does not adequately protect Applicant in view of the scope of the invention and the disclosure. Thus, to demand that Applicant limit the claimed invention to specific IL-1 delta polypeptides when it is well within the knowledge of those skilled in the art to use routine experimental techniques to make and test IL-1 delta DNA and polypeptides that are antagonists of inflammatory conditions is improper.

Moreover, Applicant respectfully submits that any characterization that might be necessary is within the purview of one of ordinary skill in the art. As evidence of this, Applicant submits herewith as Exhibit 2 an article by Smith et al. (*J. Biol. Chem.* 275(2):1169; 2000), describing four new members of the IL-1 superfamily. On page 1170, under the subheading *Structure Modeling*, Smith et al. discuss the structure modeling of the IL-1 superfamily utilizing a sequence alignment based on that known in the art for the IL-1's and IL-18, and implementing several programs that were also known in the art to further analyze and compare the structural aspects of IL-1 superfamily members (see Exhibit 3 for publication dates and abstracts for these references; copies will be provided at the Examiner's request). Thus, as shown in Figure 1, the sequence alignment of another IL-1 superfamily member, IL-1 epsilon (referred to in Smith et al. as FIL-1∈ or FIL-1ε), with other IL-1 superfamily members allows one of ordinary skill in the art to predict the beta strands of the newer IL-1 family member. Moreover, as shown in Figure 3, the amino acid sequence of IL-1 epsilon can be folded into a structure that superimposes well onto the crystal structure of IL-1 alpha and IL-1 beta, with minimal energy violations. It is a matter of routine experimentation to perform similar alignments for IL-1 delta.

Additionally, there have been several studies mapping receptor-binding sites of IL-1 family members by site-directed mutagenesis, as discussed in Evans et al. (*J. Biol. Chem.* 270(19):11477; 1995, enclosed herewith as Exhibit 4). Those of ordinary skill in the art could, by the application of routine experimentation, carry out similar studies, and verify the receptor binding sites for IL-1 delta. Moreover, the crystal structure of IL-1 receptor complexed with IL-1 beta has been deduced (Vigers et al., *Nature* 386:190; 1997, Exhibit 5), as has the crystal structure of IL-1 receptor complexed with IL-1ra (Schreuder et al., *Nature* 386:194; 1997, Exhibit 6). Such studies, performed using methods that are known in the art, can be similarly applied to IL-1 delta, allowing one of ordinary skill in the art to prepare a

genus of IL-1 delta polypeptides, including polypeptides that are 80% identical to that of SEQ ID NO:4, and that possess the function of being able to block an inflammatory response.

Accordingly, one of ordinary skill in the art could, at the time the instant application was filed, use the disclosed sequence information together with techniques that were known in the art, to predict a structure for IL-1 delta. Moreover, one of ordinary skill in the art could, at the time the application was filed, use the crystal structure of IL-1 complexed with receptor or antagonist to predict which residues are important for receptor binding. Furthermore, one of ordinary skill in the art could, at the time the application was filed, use the known mutational analysis of IL-1 family members to predict residues important for activity of IL-1 delta. Applicant respectfully submits that this characterization would allow one of ordinary skill in the art to predict variants of IL-1 delta that would be likely to retain activity. To prepare and test these variants would be a matter of routine experimentation. Applicants request that the rejection be withdrawn.

Claims 1 through 12 were rejected under 35 USC § 112, second paragraph, as allegedly being indefinite. According to the Examiner, claim 1 is indefinite for reciting hybridization "under moderately stringent conditions" without providing a precise set of conditions. Claim 1 has been amended to recite a precise set of conditions. Applicants respectfully assert that this amendment does not change the scope of the claims, but merely makes them clearer to one of ordinary skill in the art. Accordingly applicants request that this aspect of the rejection be withdrawn.

Claims 3 and 12 are alleged to be indefinite in recitation of "an inflammatory and/or autoimmune disease." According to the Examiner, recitation of "and/or" encompasses both "an inflammatory and autoimmune disease" and "an inflammatory or an autoimmune disease" and it is allegedly not clear how certain conditions can be included in the former. Applicants respectfully disagree; one of ordinary skill in the art of treating the types of conditions set forth in the claims would understand into which category certain conditions would fall. However, in an effort to be cooperative and speed allowance of the claims, claims 3 and 12 (and other claims utilizing similar language) been amended to recite "an inflammatory or autoimmune disease." Applicants respectfully assert that this amendment does not change the scope of the claims, but merely makes them clearer to one of ordinary skill in the art. Accordingly applicants request that this aspect of the rejection be withdrawn.

Claims 3 and 12 are further alleged to be indefinite in recitation of "and combinations thereof" in that it is not clear how many different combinations of all the recited diseases are intended to be treated. Applicants respectfully submit that the allegedly indefinite phrase is intended to prevent a potential infringer from circumventing the plain meaning of the claims when treating an individual afflicted with more than one inflammatory or autoimmune condition, and thus provides greater clarity to those of ordinary skill in the art than simply reciting the specific listing of conditions. Accordingly, applicants request that this aspect of the rejection be withdrawn.

Claims 4, 5 and 6 are further alleged to be indefinite in recitation of "variant amino acid sequence." The Examiner raises the question of whether the claims relates to a variant sequence or variant sequences. Claims 4, 5 and 6 have been amended to recite polypeptides selected from the group consisting of polypeptides that are at least 80% identical to the polypeptide of SEQ ID NO:4. Applicants respectfully assert that this amendment does not change the scope of the claims, but merely makes them clearer to one of ordinary skill in the art. Accordingly, applicants request that this aspect of the rejection be withdrawn.

Claims 7 through 9 are alleged to be indefinite in recitation of "selected from the group consisting of" twice in one sentence where it appears to described only one group of polypeptides. The Examiner raises the question of whether the claims relates to a variant sequence or variant sequences. Claims 7 though 9 have been cancelled, and replaced with newly added claim 13 through 15, which are believed to more clearly recite the polypeptides for use in the claimed method. Applicants respectfully assert that this amendment does not change the scope of the claims, but merely makes them clearer to one of ordinary skill in the art. Accordingly, applicants request that this aspect of the rejection be withdrawn.

Claim 2 was rejected as being dependent on an allegedly indefinite claim. Claim 1 has been amended as discussed previously. Applicants respectfully assert that this amendment does not change the scope of the claims, but merely makes them clearer to one of ordinary skill in the art. Accordingly, applicants request that this aspect of the rejection be withdrawn.

CONCLUSIONS

Claims 1 through 6 and 10 through 15 are now under consideration in the application and are believed to be in condition for allowance. Notification to this effect is respectfully requested.

If any issues of concern remain in this application, the Examiner is invited to contact the undersigned at the direct dial number given below.

Respectfully submitted,

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In the Application of: John E. Sims

Docket No.: 0315-C

Serial No.: 09/965,640

Filing Date: September 27, 2001

For: IIL-DELTA DNA AND POLYPEPTIDES

STATEMENT UNDER 37 CFR 1.825((b)

Commissioner for Patents
P. O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

Applicant submits herewith a replacement copy of the computer-readable form of the Sequence Listing in the above captioned application. The replacement copy of the computer-readable form of the Sequence Listing was prepared using Patentin V.3.2, necessitating the submission herewith of an amended copy of the paper version of the Sequence Listing. No new matter has been added to the Sequence Listing.

The paper copy of the amended Sequence Listing submitted in the present application is identical to the computer-readable form of the Sequence Listing also submitted herewith.

Please replace the previously submitted paper copy of the Sequence Listing with that submitted herewith.

Respectfully submitted,

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